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Crossmodal changes in the somatosensory vibrissa/barrel system of visually deprived animals

(cat/mouse/plasticity)

J. P. RAUSCHECKER*†‡, B. TIAN*†, M. KORTE*, AND U. EGERT†

*National Institute of Mental Health, National Institutes of Health Animal Center, Poolesville, MD 20837; and †Max-Planck-Institut für biologische Kybernetik, Tübingen, Germany

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ABSTRACT **Cats deprived of vision from birth adapt remarkably well to their situation and show little behavioral impairment. They seem to compensate for their lack of vision by relying more on their auditory and tactile senses. We report here that the facial vibrissae, which are most important for tactile orientation in many animals, show supernormal growth in both cats and mice that have been deprived of vision from birth. Furthermore, the whisker representation in the somatosensory cortical barrel field shows a concomitant enlargement in binocularly enucleated mice: individual barrels are expanded in size by up to one-third. The increased use of the vibrissae in visually deprived animals may stimulate both their own growth and, via activation of the respective neural pathways, the expansion of their central representation.**

Kittens are born with their eyes closed. When normal eye opening is prevented surgically by means of lid suture, the lids grow together permanently, which precludes all pattern vision (1). Despite their lack of vision, these cats learn to move around with little impairment and show such a high degree of behavioral normality that uninformed observers would hardly guess they could not see (1, 2). Similar compensatory plasticity has been described in young monkeys with early vision impairment (3).

There is evidence that visually deprived cats have improved auditory capacities (4, 5) and that they make very efficient use of their vibrissae (6–8). From casual observation it also appeared to us that the vibrissae were on average longer in lid-sutured cats than in normal cats. We therefore decided to determine whisker lengths and diameters quantitatively in both groups of animals.

To reduce the variance of data between animals within each group, it would be advantageous to study animals from the same litter. The small litter size in cats, however, makes this practically impossible. We decided, therefore, to study the effects of visual deprivation also on the vibrissae system in the mouse, which not only has larger litters and less genetic variability but in addition has a distinct anatomical representation of its whiskers in the central somatosensory system, the barrel field (9). We hoped that this might allow us to test for a central change in the vibrissa/barrel system possibly related to somatosensory compensation.

MATERIALS AND METHODS

Vibrissae Measurements in Cats. Whisker lengths were measured in 13 cats that had been deprived of vision by means of binocular lid suture until at least 6 months of age, and in 19 normal control animals of comparable age and weight. In addition, whisker diameter at the base was measured in 12 cats, 6 chosen randomly from each of these groups. Lid sutures had been performed by a standard procedure (1) at the Max-Planck-Institut in Tübingen, Germany, around the time of eye opening, under ketamine/xylazine anesthesia (25 mg/kg).

Whisker lengths were determined *in situ*, while the cats were anesthetized with ketamine and xylazine. Each vibrissa was stretched with a forceps and its length was taken with a dial caliper. Whisker diameters were measured under a calibrated microscope, and the vibrissae therefore had to be cut at the base. Since most deprived animals continued to be used for a number of other studies requiring intact whiskers, diameters could be determined in only a limited number of cats used for terminal experiments. Vibrissae that were obviously broken or in the process of regrowing were disregarded for analysis. Such whiskers were easily recognized both by their abnormal diameter at the tip and by their length when compared with the neighboring vibrissae on either side.

Barrel Measurements in Mice. Six mouse pups from three litters were binocularly enucleated under ketamine anesthesia (25 mg/kg) during the first postnatal week. A small incision was made across the bulbus on both sides through the still-closed eye lids and the lens and vitreous body were removed. The enucleated animals were raised together with seven normal littermates until 2–3 months of age. (It seemed important to use pigmented rather than albino mice, since the latter are known to have a genetic defect causing impaired vision.) No significant difference in body weight was found between the two groups, although there was a tendency for the normal animals to be slightly heavier ($P < 0.1$). To study the barrel field in the somatosensory cortex, the fresh brains were taken out, flat-mounted between two glass slides with 1-mm spacers (10), and fixed by immersion in 2.5% paraformaldehyde/1.5% glutaraldehyde. No difference in fresh brain weight was found between normal and enucleated animals. The flat mounts were cut into 50-μm-thick sections and prepared for cytochrome oxidase histochemistry (11). The individual "barrels," which show up as hollows in Nissl-stained sections for reasons of cytoarchitectonic specialization, appear as filled dark "clusters" with cytochrome oxidase staining. For simplicity, we will nevertheless refer to these clusters as barrels.

Vibrissae Measurements in Mice. The vibrissae were cut and measured in four enucleated and four normal mice from two litters. Lengths and diameters were determined in a double-blind procedure by a person who had no information about the history of the individual animals.

Statistical Analysis. Statistical analysis of length and diameter distributions of the whiskers and of barrel size was done either by means of a *t* test (assuming a normal distribution) or by means of the binomial test in the following way. Difference distributions (deprived minus normal) were calculated for

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‡To whom reprint requests should be addressed at: National Institutes of Health Animal Center, National Institute of Mental Health, P.O. Box 289, Poolesville, MD 20837.

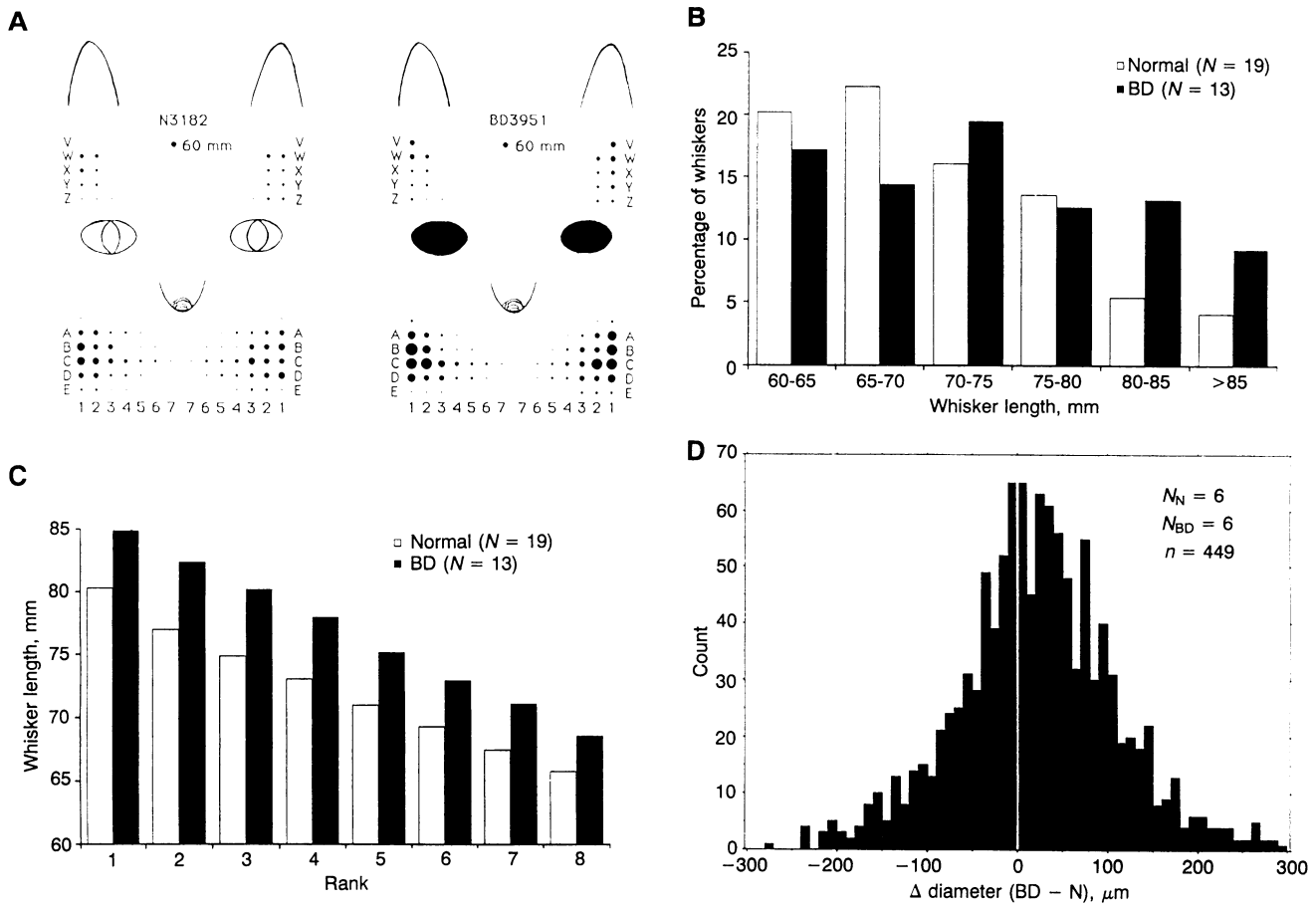

FIG. 1. Whisker size in cats after long-term visual deprivation. (*A*) Two examples of whisker pads are depicted schematically, one from a normal cat (left) and one from a cat that had been binocularly deprived (BD) by lid suture from birth until 2 years of age. Each dot represents one vibrissa in a scheme adapted from Woolsey and Van der Loos (ref. 9). The size of the dot corresponds to the length of the whisker. It can be seen that especially whiskers in columns 1 and 2, which are the longest normally, are even longer in the visually deprived cat. (*B*) The length distribution of whiskers over 60 mm is shown for normal (open bars) and BD (filled bars) cats. The BD animals have significantly more whiskers over 80 mm in length ($P < 0.01$; Kolmogorov–Smirnov test). (*C*) The same data are displayed as a rank distribution from the longest to the eighth-longest vibrissae of each animal in the two groups. (*D*) The distribution of differences in whisker diameter between binocularly deprived cats and normal cats was calculated as follows. Diameter distributions were assembled separately for each whisker position and group. Then the distributions from each group and position were compared by calculating the difference between them whisker by whisker. This procedure delivers one single distribution for all differences (BD − N) in all positions between the two groups of animals and eliminates the systematic variation of whisker size with position. The difference distribution can then be analyzed statistically by means of the binomial test. N_N and N_{BD}, number of normal and BD animals; *n*, number of vibrissae analyzed.

each whisker or barrel position. With the null hypothesis being that there is no difference between the two groups, symmetrical distributions would be found, and the binomial test would show no significant difference.

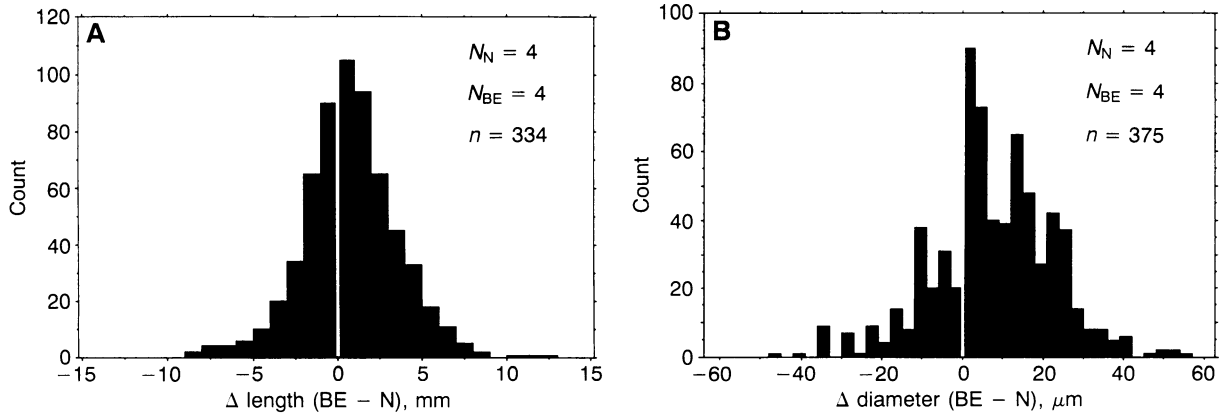

FIG. 2. Whisker size in mice after early binocular enucleation (BE). Difference distributions for whisker length (*A*) and diameter (*B*) were assembled in the same way as in Fig. 1*C*. Both distributions are skewed to the right, indicating that the enucleated mice have longer and thicker whiskers than their normal littermates ($P < 0.0001$; binomial test). N_{BE}, number of BE animals.

RESULTS

Cat Vibrissae. An example of whisker length of one cat from each group (binocularly deprived and normal) is depicted in Fig. 1*A*. The length distribution of whiskers from all animals shows that the visually deprived cats had more vibrissae with a length of over 80 mm (Fig. 1*B*). In a rank distribution for the longest up to the eighth-longest vibrissa from each animal, a consistent difference was found between the two groups, with whiskers from the deprived cats being about 5 mm longer (Fig. 1*C*).

Vibrissae in different positions on the mystacial pad have different sizes, with the most lateral/caudal ones usually being the longest and thickest (see Fig. 1*A*). To account for this systematic variation of size with position, difference distributions (binocularly deprived − normal) for whisker lengths and diameters were calculated. The distribution for diameter is displayed in Fig. 1*D*. A preponderance of values to the right of zero indicates that the binocularly deprived cats had thicker whiskers ($P < 0.0001$; binomial test). Similar results were obtained with this analysis for whisker length ($P < 0.0002$). When the single distributions are compared for each position separately, the most significant differences, for both whisker length and diameter, are found in the lateral and caudal positions, corresponding in particular to columns 1 and 2.

Mouse Vibrissae. The difference in whisker length and diameter between the two groups of mice was analyzed and plotted in the same way as for the cats. Again, both distributions (Fig. 2) were skewed to the right, meaning that the enucleated mice had longer and thicker whiskers than their normal littermates ($P < 0.0001$; binomial test). Comparisons within and between litters of the same group did not show any significant differences. Position-specific analysis revealed that the most significant differences between groups were, as in cats, present for the longest whiskers, which are in the most lateral and caudal positions.

Mouse Barrel Field. The brain sections containing the barrel field were analyzed with the aid of an image-analysis system (IMAGE, National Institute of Mental Health) based on a Macintosh IIfx computer. Fig. 3 demonstrates the procedure for extracting the size of each barrel in one hemisphere. The size distributions for all barrels in both groups are given in Fig. 4*A*. Overall, barrels were larger in the enucleated animals by 15% ($P < 0.0001$; t test). When position-specific comparisons were made, expansions of up to 33% were found. Difference distributions for individual barrel positions were analyzed by means of the binomial test (Fig. 4*B*). The most consistent individual differences were present for the large barrels in columns 1 and 2 corresponding to more lateral and caudal whiskers, which had also shown the most excessive growth both in cats and in mice.

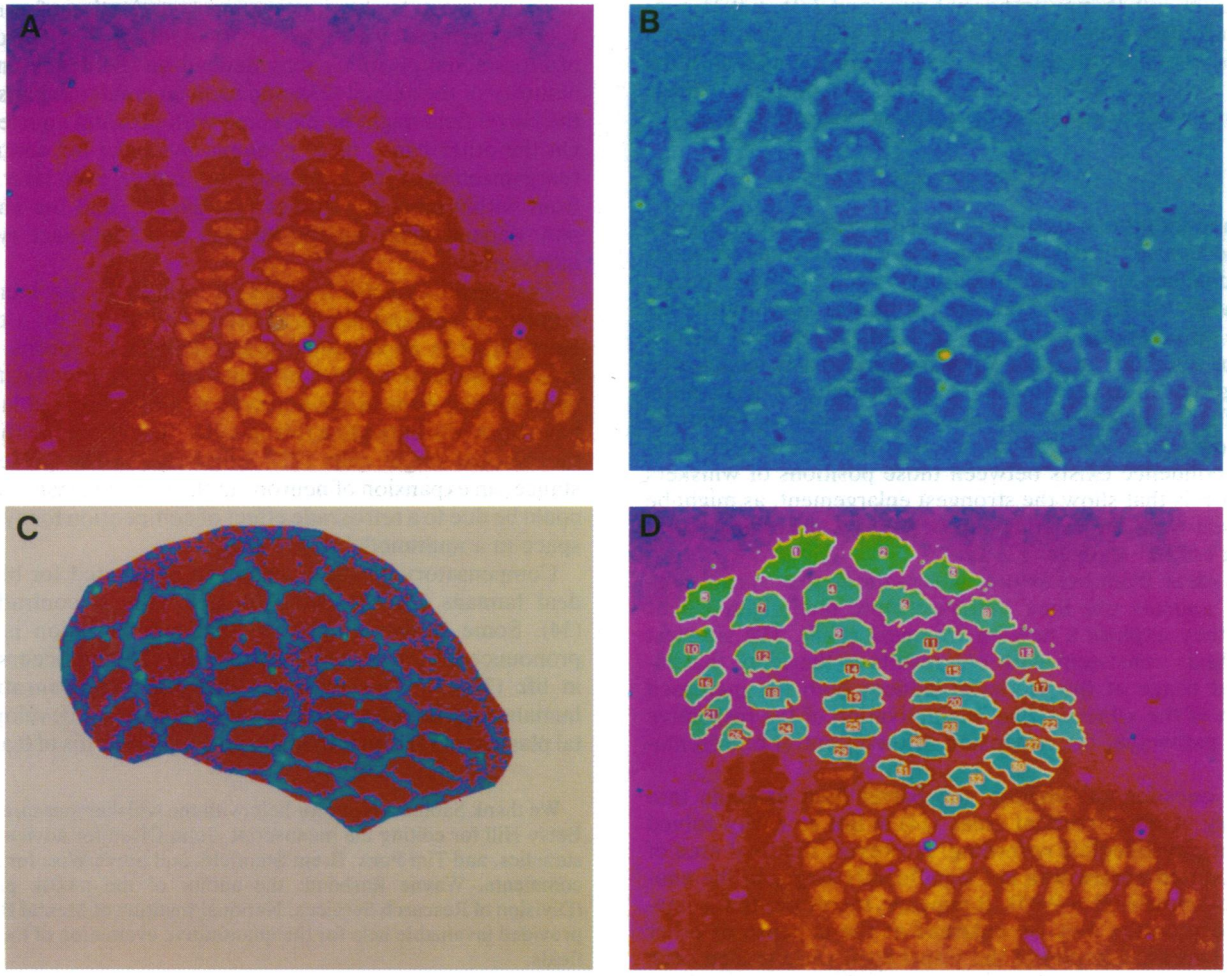

FIG. 3. "Barrels" in a flat mount of mouse somatosensory cortex stained for cytochrome oxidase and processed for evaluation of areas with a computerized imaging system. (*A*) The original section (from a binocularly enucleated mouse) is digitized onto a Macintosh IIfx with a high-resolution camera and displayed in pseudocolor representing different levels of luminance. (*B*) A background-corrected version of the same section. A spatial low-pass filter eliminates unwanted gradients caused by uneven illumination or staining. The same filter is used for every section. (*C*) An area of interest is defined, for which a threshold is set automatically by the program as mean luminance plus a constant. (*D*) Using this same standard threshold for every section, the program converts the image into a binary format, draws the outlines for each individual barrel, and automatically determines its size.

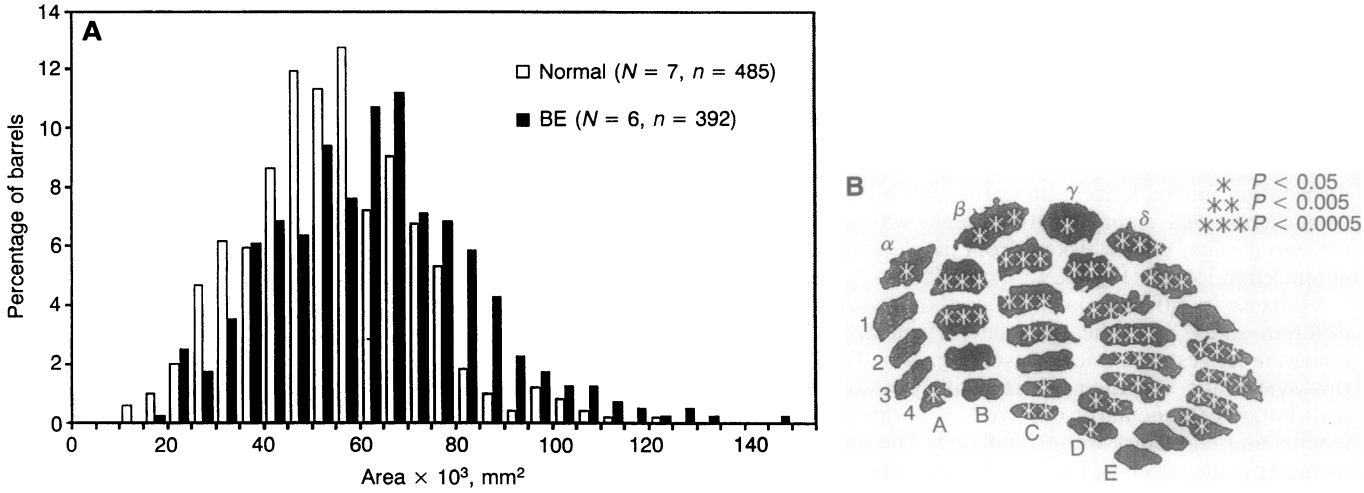

FIG. 4. Difference in barrel size of somatosensory cortex between normal and binocularly enucleated (BE) mice. (*A*) Size distribution of all barrels in the two groups. The largest barrels are even larger in the BE animals, which causes their distribution to be shifted to the right ($P < 0.0001$; *t* test). Comparisons within and between litters of the same group did not show any significant differences. (*B*) Results of comparisons between individual barrels from the two groups. Difference distributions were calculated as in Fig. 1*C* and analyzed by means of the binomial test. Significance levels are displayed as asterisks. The large barrels in rows D and E and in columns 1 and 2 seem to profit most.

In addition to the single barrels we also measured the total size of the barrel field in each hemisphere, which was found to be 2.99 ± 0.35 mm² in normal mice and 3.35 ± 0.31 mm² in enucleated mice ($P < 0.01$; *t* test). The septa between barrels were not enlarged ($P > 0.1$). Average darkness of the barrel field (corresponding in part to cytochrome oxidase activity) was not significantly different between groups.

DISCUSSION

We have found that in two mammalian species as diverse as cat and mouse, visual deprivation from birth leads to significant changes in the somatosensory system. In both species the facial vibrissae, which are of utmost importance for tactile orientation, are longer and thicker than in normal control animals. In mice that are binocularly enucleated during their first week of life, a concomitant increase in the size of individual barrels representing the vibrissae within the somatosensory cortex is found. Furthermore, a very good correspondence exists between those positions of whiskers and barrels that show the strongest enlargement, as might be expected from the relationship between whisker and barrel size in normal animals (12, 13).

It is clear from behavioral observations that visually deprived animals use their vibrissae more than sighted ones when they explore a new environment (6–8). The simplest hypothesis consistent with our results is therefore that increased usage of the vibrissae induces both the increased growth of the vibrissae and, via activation of the respective neural pathways, the expansion of their central representation.

The question of whether the barrel field expands into territory of other cortical areas (14) is not so easily solved without physiological recording. However, the total area of flat-mounted cortex was not significantly larger in the enucleated animals ($P > 0.05$). It appears, therefore, that somatosensory cortex may be enlarged at the expense of other cortical areas. Atrophy of the visual cortex has indeed been demonstrated after early binocular enucleation in monkeys (15–17) and after dark-rearing in mice (18). In the latter case, a concomitant hypertrophy of auditory cortex has also been reported.

There are various other examples of crossmodal plasticity. Visually deprived animals show an enhanced capacity in auditory localization (4, 5) and have increased numbers of auditory-responsive neurons in their midbrain (19, 20). Other studies have indicated that binocular enucleation or visual deprivation can lead to innervation or activation of normally visual structures by somatosensory input (21, 22). The degree of crossmodal plasticity may depend on the developmental maturity of the animal (23), and an even greater expansion of the barrel field might be expected with prenatal enucleation. On the other hand, there is ample evidence for continuing reorganization of the somatosensory cortex even later in life from within-modality studies (14, 24–26), and the changes may depend more on the species and the exact type of intervention.

The barrel expansion could be caused by an increased number of neurons due to reduced cell death, by a denser neuropil, or by an increased size of individual neurons. In the lateral geniculate nucleus of monocularly deprived cats, the different cell sizes in the deprived and nondeprived laminae have been attributed to a retrograde effect of competition for the cortical target cells (27). Similarly, in the present instance, an expansion of neurons in the somatosensory cortex could be due to a retrograde effect of competition for synaptic space in a multimodal target area.

Compensatory plasticity has been postulated for blind or deaf humans (28–33), although not without contradiction (34). Some studies emphasize that compensation is more pronounced if the onset of sensory deprivation occurs early in life (31–33). This indicates that such compensation in humans may be related to basic mechanisms of developmental plasticity (35) rather than to some higher forms of learning.

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